Parkinson's Disease and Exposure to Infectious Agents and Pesticides and the Occurrence of Brain Injuries: Role of Neuroinflammation

Bin Liu,* Hui-Ming Gao, and Jau-Shyong Hong

Neuropharmacology Section, Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences/National Institutes of Health, Research Triangle Park, North Carolina, USA

Idiopathic Parkinson's disease (PD) is a devastating movement disorder characterized by selective degeneration of the nigrostriatal dopaminergic pathway. Neurodegeneration usually starts in the fifth decade of life and progresses over 5–10 years before reaching the fully symptomatic disease state. Despite decades of intense research, the etiology of sporadic PD and the mechanism underlying the selective neuronal loss remain unknown. However, the late onset and slow-progressing nature of the disease has prompted the consideration of environmental exposure to agrochemicals, including pesticides, as a risk factor. Moreover, increasing evidence suggests that early-life occurrence of inflammation in the brain, as a consequence of either brain injury or exposure to infectious agents, may play a role in the pathogenesis of PD. Most important, there may be a self-propelling cycle of inflammatory process involving brain immune cells (microglia and astrocytes) that drives the slow yet progressive neurodegenerative process. Deciphering the molecular and cellular mechanisms governing those intricate interactions would significantly advance our understanding of the etiology and pathogenesis of PD and aid the development of therapeutic strategies for the treatment of the disease. *Key words:* bacterium, cytokine, dopamine, environmental factor, free radical, head injury, microglia, Parkinson's disease, pesticide, virus. *Environ Health Perspect* 111:1065–1073 (2003). doi:10.1289/ehp.6361 available via *http://dx.doi.org/* [Online 14 May 2003]

Parkinson's disease (PD) is a degenerative neurologic disorder characterized by progressive degeneration of the nigrostriatal dopaminergic pathway that regulates body movements (Olanow and Tatton 1999). Degeneration of the nerve terminals in the striatum (ST) and the neuronal cell bodies of dopamine-containing neurons in the substantia nigra (SN) eventually leads to the development of movement disorders, including resting tremor, rigidity, bradykinesia, and gait disturbance (Jellinger 2001). In addition to the degeneration of dopaminergic neurons in the SN, postmortem analysis of the brains of PD patients has frequently detected the existence of cytoplasmic inclusions in the SN neurons, also known as Lewy bodies (Holdorff 2002; Schiller 2000). Formation of Lewy bodies is a pathologic hallmark of PD and an affirmative postmortem diagnostic marker (Takahashi and Wakabayashi 2001).

Ever since its initial description by British physician James Parkinson in 1817, the etiology of PD as well as the precise mechanism of action underlying the selective destruction of the nigrostriatal dopaminergic pathway has remained unknown (Di Monte and Lawler 2001; Langston 2002; Mulhearn 1971). Currently, clinical diagnosis of PD is based on movement-related behavioral abnormalities (Rao et al. 2003; Sethi 2002). However, the absence of distinct biomarkers for the prognosis of the disease, because of the lack of clear understanding of the disease process, has significantly hampered efforts to identify and treat PD patients early in the disease course. At the present time, dopamine replacement therapy using levodopa is the most widely used approach in the treatment of clinically diagnosed and often advanced PD patients (Hornykiewicz 2002; Katzenschlager and Lees 2002; Miyasaki et al. 2002). However, the efficacy of such neurotransmitter replacement therapy has been limited because of resistance and loss of response (Kostrzewa et al. 2002; Muller 2002).

Advances made in the last several decades at the forefront of molecular cloning, biochemical characterization, pathology analysis, and epidemiologic studies have come to the general consensus that most (> 95%) PD cases are sporadic and have a late onset (Tanner 2003). A small faction (< 5%) of cases is characterized by early onset, and these mostly occur in familial clusters (Mizuno et al. 2001). Development of parkinsonism syndrome in those individuals has been attributed to mutations in several recently identified genes, including *parkin* and α*-synuclein* (de Silva et al. 2000; Gwinn-Hardy 2002). In contrast, development of idiopathic PD may represent the final outcome of a complex set of interactions among the innate vulnerabilities of the nigrostriatal dopaminergic system, potential genetic predisposition, and exposure to environmental toxicants. There is growing recognition of the role of inflammation in the brain (neuroinflammation) in the pathogenesis of PD (McGeer et al. 2001). Neuroinflammation in the brain can be induced by exposure to either infectious agents or toxicants. Neuroinflammation can also occur as a sequela to neurotoxicant-elicited neuronal damage or injuries in the brain, a process called reactive gliosis (Liu and Hong 2003). In this article, we review the literature on the potential impact on the development of idiopathic PD of environmental factors such as exposure to infectious agents and pesticides and early-life occurrence of brain injuries. More important, we will attempt to establish a possible link between early-life neuroinflammation and late life development of idiopathic PD.

Immune Cells in the Brain

Inflammation in the brain involves primarily the activity of two types of glial cells: microglia and astrocytes. Microglia are the resident immune cells in the brain (del Rio-Hortega 1993). During late embryonic and early postnatal brain remodeling and maturation, microglia are involved in the programmed elimination of neural cells (Barron 1995; Milligan et al. 1991). In mature brains, resting microglia exhibit a characteristic ramified morphology and serve the critical role of immune surveillance. As an important line of defense in the brain, microglia become readily activated in response to injuries to the brain or to immunologic stimuli (Kreutzberg 1996; Liu and Hong 2003; Streit et al. 1988, 1999). Activated microglia undergo dramatic morphologic changes, metamorphosing from resting ramified microglia into activated amoeboid microglia (Kreutzberg 1996). They also exhibit increased expression of surface molecules such as complement receptors and major histocompatibility complex (MHC) molecules (Graeber et al. 1988; Oehmichen and Gencic 1975). At the same time, activated microglia release a variety of soluble factors. Although activated microglia are known to produce several trophic factors (Barde 1989; Lindsay et al. 1994; Streit et al. 1999), most of the factors released by activated microglia are proinflammatory and potentially cytotoxic.

Astrocytes, under physiologic conditions, provide glia–neuron contact, maintain ionic

Address correspondence to Bin Liu, NIEHS/NIH, Mail Drop F1-01, P.O. Box 12233, Research Triangle Park, NC 27709 USA. Telephone: (919) 541-4024. Fax: (919) 541-0841. E-mail: liu3@niehs.nih.gov

*Current address: Dept. of Pharmacodynamics, JHMHC, College of Pharmacy, University of Florida, P.O. Box 100487, Gainesville, FL 32610 USA. E-mail: bliu@cop.ufl.edu

We thank M. Patton and M. Block for reading the manuscript.

The authors declare they have no conflict of interest.

Received 31 March 2003; accepted 14 May 2003.

homeostasis, buffer excess neurotransmitters, and secrete neurotrophic factors (Aloisi 1999; Hansson and Ronnback 1995; Vernadakis 1988). In response to immunologic challenges and brain injuries, astrocytes also become activated (Aloisi 1999; Tacconi 1998). In the course of activation, astrocytes up-regulate the expression of cell-type–specific proteins such as the glial fibrillary acidic protein (Diedrich et al. 1987). In addition, they secrete neurotrophic factors (Friedman et al. 1990; Lindsay et al. 1994) and several proinflammatory cytokines.

Microglia as the Primary Contributor of Proinflammatory and Neurotoxic Factors

In terms of the release of proinflammatory and cytotoxic factors, activated microglia differ significantly from activated astrocytes in several respects. First, the repertoire of factors produced by activated microglia is far more complex than that of activated astrocytes (Figure 1). For example, bacterial endotoxin lipopolysaccharide (LPS)–stimulated production of tumor necrosis factor-α (TNF-α) appears to be limited to microglia and has not been observed in astrocytes (Giulian and Baker 1986; Lee et al. 1993; Sawada et al. 1989). Astrocytes, but not microglia, failed to respond to β-amyloid peptide–stimulated production of superoxide free radicals (Qin et al. 2002). Second, of the factors produced by both cell types, microglia produce a significantly larger quantity of most such factors than do astrocytes. For instance, LPS-stimulated microglia produced several-fold higher amounts of nitrite, an indicator of the production of nitric oxide (NO), than did LPS-stimulated astrocytes (Iravani et al. 2002; Liu et al. 2002). Similarly, the LPS-stimulated production of interleukin-1β (IL-1β) was far more prominent in microglia than in astrocytes (Fontana et al. 1982; Giulian et al. 1986; Hetier et al. 1988; Lee et al. 1993). A notable exception may be that activated astrocytes, as well as activated microglia, produce abundant quantities of prostaglandins (PGs), such as PGE and PGD (Alafiatayo et al. 1994; Fontana et al. 1982; Minghetti and Levi 1995). Third, in response to immunologic stimuli, the production kinetics of proinflammatory factors is different. Microglia usually respond faster than astrocytes. For example, LPS-induced production of NO occurred within the first 6–12 hr in microglia, compared with a much delayed time point (24 hr) in astrocytes (Liu et al. 2002). Interestingly, astrocytes appear to rely on secondary responses to produce certain proinflammatory factors. For example, human astrocytes that were insensitive to LPS stimulation responded well to stimulation by IL-1β and produced fair quantities of TNF-α and IL-6 (Lee et al. 1993). These observations strongly imply that microglia, as the first line of response to immunologic challenges in the brain, play the primary role in the brain inflammatory process and therefore are, under pathologic conditions, the predominant contributor to the inflammation-mediated neurodegenerative process.

Overproduction and Accumulation of Proinflammatory and Neurotoxic Factors Are Deleterious to Neurons

Numerous *in vitro* and *in vivo* studies have demonstrated that the production and accumulation of proinflammatory and cytotoxic factors by activated glia have an impact on neurons, inducing neurodegeneration. Neurotoxicity has been attributed to high levels of NO (Chao et al. 1992; Dawson et al. 1994; Gao et al. 2002b; Gayle et al. 2002; Jeohn et al. 2000), IL-1β (Downen et al. 1999; Gayle et al. 2002; Hu et al. 1997; Ma et al. 2002; Wu et al. 2002), IL-6 (Ladenheim et al. 2000), TNF-α (Downen et al. 1999; Gayle et al. 2002; McGuire et al. 2001), and reactive oxygen species (ROS) such as superoxide anions (Gao et al. 2002a, 2002b; Liu et al. 2000a; Qin et al. 2002; Xie et al. 2002). Besides being individually toxic to neurons, NO and superoxide may form more toxic intermediates such as peroxynitrite (Beckman and Crow 1993; Xie et al. 2002). Individual factors also may work in concert to induce synergistic neurotoxicity, a scenario that may bear a closer resemblance to the *in vivo* neurodegenerative process (Chao et al. 1995; Jeohn et al. 1998). Conflicting results have been reported regarding the involvement of prostanoids in inflammation-mediated neurodegeneration. On the one hand, inhibitors of cyclooxygenases and/or 5-lipoxygenase have been shown to protect neurons from inflammation-mediated toxicity (Araki et al. 2001; Klegeris and McGeer 2002). On the other hand, exogenous PGE_2 has been reported to attenuate LPS-induced neurotoxicity (Kim et al. 2002). Nevertheless, it is generally believed that the accumulation of a variety of proinflammatory and neurotoxic factors released from activated microglia eventually results in neurodegeneration (Liu and Hong 2003).

In reference to dopaminergic neurodegeneration, it is especially important to note that the SN dopaminergic neurons are characteristically sensitive to insults by a variety of external factors because of their reduced antioxidant capacity; their high content of dopamine, melanin, and lipids that are prone to oxidation; and potential defects in mitochondrial function (Greenamyre et al. 1999; Jenner and Olanow 1998). Furthermore, the SN area of the brain is particularly rich in microglia (Kim et al. 2000; Lawson et al. 1990). Hence, SN dopaminergic neurons, residing in a microglia-rich environment (Kim et al. 2002; Lawson et al. 1990), are especially vulnerable to attacks imposed by factors produced by activated microglia.

Findings Associating Brain Inflammation with the Pathogenesis of PD

The initial findings linking inflammation in the brain with the pathogenesis of PD have

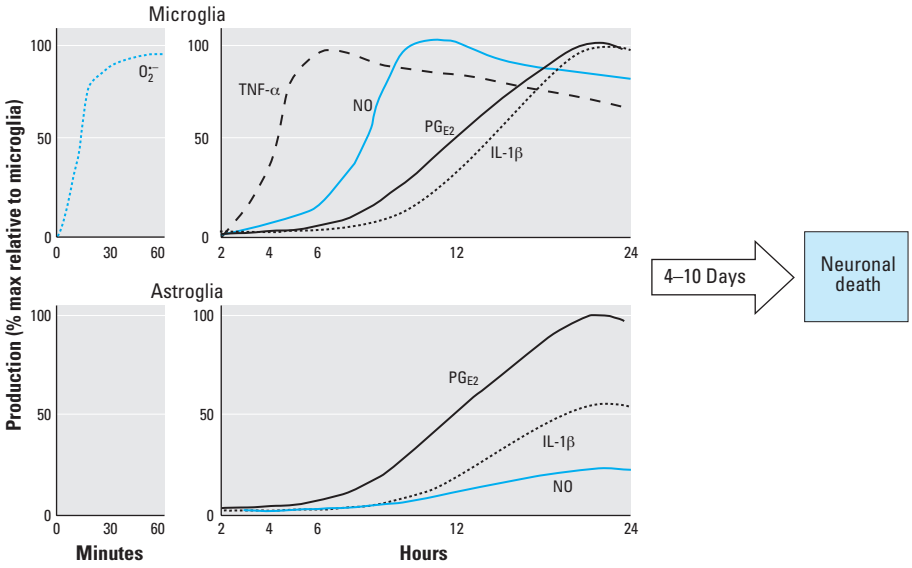

Figure 1. Differential production of proinflammatory factors by microglia and astroglia in response to stimulation by LPS. Abbreviations: max, maximum; $O_2^{\bullet-}$, superoxide. LPS-activated microglia and astroglia differ in the variety, quantity, and kinetics of proinflammatory factors they produce. The differences may determine their contribution to the neurodegenerative process. Factors produced by activated glial cells are known to be able to induce secondary responses, in an autocrine and/or paracrine fashion, to produce a variety of additional soluble factors.

been derived from postmortem analysis of the nigra of PD patients. In 1988, McGeer et al. reported the detection of large populations of MHC [human leukocyte antigen (HLA)-DR]-positive reactive microglia in the SN of the PD brains they analyzed. Since then, numerous studies have reported the detection of significantly elevated levels of a variety of proinflammatory factors in the SN, ST, or cerebrospinal fluid (CSF; Table 1). Those factors included components of the innate immune response such as complement proteins (Yamada et al. 1992) and cytokines such as IL-1, IL-2, IL-6, and TNF-α (Blum-Degen et al. 1995; Hunot et al. 1999; Mogi et al. 1994a, 1994b, 1996; Muller et al. 1998; Stypula et al. 1996). In addition, inducible NO synthase (iNOS)–positive glial cells also have been detected in the midbrain region of PD brains (Hunot et al. 1996). These observations have clearly demonstrated that inflammation, particularly microglial activation, is involved in the pathogenesis of PD. In addition, molecular genetic analysis of polymorphisms in the genes for IL-1, IL-6, and TNF-α as well as the TNF-α receptor gene of PD patients and matched controls further supports the involvement of cytokines in the pathogenesis of PD (Kruger et al. 2000; McGeer et al. 2002; Nishimura et al. 2000, 2001; Schulte et al. 2002). Nevertheless, because most of the changes were detected in the terminal stage of the disease, it has remained an open question whether the observed glial activation was merely a consequence of the reactive glial response to neuronal loss. Clearly, additional evidence will be needed to establish that glial activation, especially microglial activation, is involved in an earlier stage of dopaminergic neurodegeneration during the PD pathogenetic process.

Is Exposure to Infectious Microorganisms a Risk Factor for PD?

For several decades, infectious agents have been suspected to be risk factors for PD. Epidemiologic studies have associated early-life viral infections to postencephalitic PD; case reports, on the other hand, tend to relate viral infections to the development of acute parkinsonism (Bhatt et al. 2000; Duvoisin and Yahr 1972; Elizan and Casals 1991; Ghaemi et al. 2000; Maurizi 1985; Pradhan et al. 1999). Experimentally, exposure of neonatal Fisher 344 rats to Japanese encephalitis virus can induce the degeneration of SN dopaminergic neurons, development of movement disorders resembling human PD, and occurrence of gliosis in the SN (Ogata et al. 1997). However, identification of a specific causative viral agent (DNA or antigens) in humans has so far proven elusive (Schwartz and Elizan 1979; Wetmur et al. 1979). It is possible that viral infections alone are not sufficient to initiate the development of idiopathic human PD, but viral infection–associated inflammation at an early stage of life may well play a role in the pathogenesis of the disease. However, the probability of unearthing "footprints" (i.e., viral DNA and/or antigens) of early-life viral infections in postmortem analyses of PD brains might be exceptionally low.

Besides viruses, infections by bacterial pathogens have also been proposed to play a role in the development of PD. Because of the increased frequency of peptic ulcers observed in some PD patients, infection by *Helicobacter pylori* has been one such candidate bacterium (Altschuler 1996). Small-scale paired-case studies appear to support the hypothesis (Charlett et al. 1999; Dobbs et al. 2000). However, solid evidence and experimental animal models are lacking to establish a role for *H. pylori* infection in the pathogenesis of PD. Of particular interest, however, is the demonstration by Kohbata and Beaman (1991) that mice injected with *Nocardia asteroides*, a common bacterium in the soil, developed PD-like syndromes. Although the relevant mechanism of action remains unknown, subsequent *in vitro* and *in vivo* studies showed that infection with one strain of *Nocardia* (GUH-2) resulted in apoptotic death of SN dopaminergic neurons (Tam et al. 2002). Although the involvement of glial cells in the neurotoxic process was not established (Beaman and Beaman 1993) and a serologic case–control study could not associate *Nocardia* exposure to human PD (Hubble et al. 1995; Kohbata and Shimokawa 1993), continued research is warranted.

Table 1. Detected indicators for microglial activation in the postmortem analysis PD brains.

Marker	Location	Reference
HLA-DR–positive microglia	SN	McGeer et al. 1988
iNOS–positive glia	SN	Hunot et al. 1996
Complement–positive Lewy bodies	SN	Yamada et al. 1992
iNOS	SN	Hunot et al. 1996
IL-1	SN/ST/CSF	Mogi et al. 1994a Blum-Degen et al. 1995 Hunot et al. 1999
IL-2	ST/CSF	Mogi et al. 1996 Stypula et al. 1996
IL-6	ST/CSF	Mogi et al. 1994a Muller et al. 1998 Blum-Degen et al. 1995
TNF-α	SN/ST/CSF	Mogi et al. 1994b Hunot et al. 1999
Interferon γ	SN	Hunot et al. 1999

Inflammogen-Induced Dopaminergic Neurodegeneration: Experimental Models of Inflammation-Related PD

To directly test the hypothesis that inflammation in the brain can result in selective dopaminergic neurodegeneration, a number of groups have used LPS to evoke inflammation in the brain. Initially, LPS was injected directly in a bolus manner into the SN area of rat brains (Castano et al. 1998; Hsieh et al. 2002; Iravani et al. 2002; Liu et al. 2000b; Lu et al. 2000). Dramatic degeneration of the nigrostriatal dopaminergic pathway was observed in those animals receiving the LPS injections. However, this single application–induced neurodegeneration was not selective to dopaminergic neurons. More important, inflammation (e.g., microglial activation) induced by the relatively large quantity of LPS (microgram levels) was too fast and too robust to enable us to clarify the temporal relationship between microglial activation and dopaminergic neurodegeneration (Liu et al. 2000b). A chronic LPS infusion model was subsequently established (Gao et al. 2002b). In this model, LPS was chronically infused for 2 weeks at a rate of 5 ng/hr into the SN region of rat brains using an epidermal osmotic minipump. Maximal microglial activation occurred in the first 2 weeks, but significant degeneration of SN dopaminergic neurons did not manifest until 4–6 weeks after the LPS infusion. In *in vitro* studies using mesencephalic neuron–glia cultures, inhibition of microglial activation and reduction of the production of microglia-derived neurotoxic factors significantly attenuated the LPS-induced dopaminergic neurodegeneration (Gao et al. 2002b; Liu et al. 2000a). In addition to infusion of LPS into adult rodent brains, *in utero* exposure of developing fetuses to LPS results in degeneration of the nigrostriatal dopaminergic pathway in neonates (Ling et al. 2002). These studies thus provide a tentative mechanistic link between the occurrence of inflammation in the brain and dopaminergic neurodegeneration and also provide experimental evidence to suggest that the occurrence of neuroinflammation in early life, if not an inducer by itself, may represent a risk factor for development of PD later in life.

Traumatic Brain Injury and Development of PD

As with the potential association of infection with development of PD, the possible correlation between the occurrence of closed head

injury with PD development rests largely on information obtained through epidemiologic studies and physicians' case reports (Ben-Shlomo 1997; Factor et al. 1988). Analysis of the medical histories of a large group of World War II veterans pointed to an association between the occurrence of severe antecedent head injuries and the development of PD in later life (Plassman et al. 2000). This notion is supported by several other studies, including several case–control studies, that have identified head injury as a major risk factor for the development of PD (Stern et al. 1991; Taylor et al. 1999; Tsai et al. 2002). In contrast, several other studies failed to establish a correlation between the occurrence of head injuries and later development of PD (Goetz and Pappert 1992; McCann et al. 1998; Williams et al. 1991). This contradiction may reflect the difficulty of designing large-scale epidemiologic studies, identifying reliable parameters for measurements, and interpreting complex data. Nevertheless, numerous case reports have described episodes of traumatic brain injuries with the occurrence of an acute-phase parkinsonism (Bhatt et al. 1999; Nayernouri 1985) or later life development of PD (Doder et al. 1999; Geiger 1975; Louis et al. 1996). Worth noting is the hypothesis of so-called "Boxer's parkinsonian syndrome," which proposes that boxers, because of their professionally related higher chance of suffering head injuries, appear to have a higher incidence of Parkinson-like movement disorders (Friedman 1989; Guterman and Smith 1987; Unterharnscheidt 1995).

Although the mechanism underlying this head trauma–related development of permanent damage to the nigrostriatal pathway remains unclear, it is possible that the initial neuronal damage leads to the activation of glial cells, whose activity may exacerbate the neurodegenerative process. This may be especially true in late-onset cases of PD after brain injuries. Using an animal model of closed head injury, Shohami et al. (1997) have demonstrated significant elevations in the levels of a number of cytokines (including IL-1, IL-6, and TNF-α) after head injury in rats. The production and accumulation of those proinflammatory factors may exacerbate the neuronal damage initially induced by the head injury. A fundamental yet unsolved issue, however, is the identity of the responsible initiating factor(s) that is presumably released from injured neurons and that stimulates the activation of glial cells. Over the years, a variety of soluble factors as well as cell–cell adhesion molecules have been proposed and/or implicated (Chang et al. 2000a, 2000b; Giulian and Ingeman 1988; Giulian et al. 1991; Raivich et al. 1999). Continued search for such factors and elucidation of the molecular mechanism responsible for the neuronal injury–induced reactive gliosis will advance our understanding of the complex pathogenesis of PD.

Exposure to Pesticides and Development of PD

Exposure to agrochemicals, particularly pesticides, has long been suggested as a risk factor for PD (Barbeau et al. 1985; Engel et al. 2001; Gorell et al. 1998; Herishanu et al. 2001; Hubble et al. 1993; Petrovitch et al. 2002; Ritz and Yu 2000; Seidler et al. 1996; Semchuk et al. 1992; Tuchsen and Jensen 2000). The identification of 1-methyl-4-phenyl-1,2,3-tetrahydropyridine (MPTP), a by-product of illicit heroin synthesis, as the culprit that induced Parkinson syndromes in humans (Langston et al. 1983) has significantly intensified the search for environmental factors as potential causes of PD (Lewin 1985). To date, exposure to several classes of pesticides has been reported to result in dopaminergic neurotoxicity in animal models, and such pesticides have hence been proposed as potential risk factors in humans (Table 2).

The structural similarity between 1-methyl-4-phenylpyridinium ion (MPP^+), the active metabolite of MPTP, and a common herbicide, 1,1′-dimethyl-4,4′-bypyridinium (paraquat), prompted speculation that paraquat might be a dopaminergic neurotoxicant. Barbeau et al. (1985) reported that paraquat, like MPTP, induced parkinsonian behavioral changes and dopamine depletion in the northern leopard frog (*Rana pipiens*). Subsequently, it was reported that exposure to pesticides including paraquat was positively correlated with increased incidence of PD in patients in parts of Canada (Rajput et al. 1987). Similar observations were reported in farming communities in Taiwan (Liou et al. 1997). Research conducted in the last decade has provided a more in-depth understanding of the dopaminergic neurotoxicity of paraquat. Intracerebral injection of paraquat resulted in loss of SN dopaminergic neurons, depletion of dopamine in the SN, and an elevated response to apomorphine-induced rotational behavior (Liou et al. 1996). The reported effects of systemically administered paraquat, on the other hand, have been less consistent. For example, Brooks et al. (1999) reported that systemic administration of paraquat to C57BL/6 mice resulted in the loss of SN dopaminergic neurons, degeneration of ST dopaminergic fibers, and reduced ambulatory activity. In contrast, McCormack et al. (2002) reported that mice that underwent repeated systemic administration of paraquat exhibited a selective loss of SN dopaminergic neurons without a reduction in ST dopamine content. Instead, enhanced dopamine synthesis in the ST, which was attributed to a possible compensatory mechanism, was observed (McCormack et al. 2002). Mechanistically, the ability of paraquat to induce free radical formation (Fukushima et al. 1995; Yumino et al. 2002), facilitate α-synuclein fibrillation (Uversky et al. 2001), and induce apoptotic cell death (Chun et al. 2001) has been associated with its dopaminergic neurotoxicity.

Another class of agrochemicals that have been found to possess dopaminergic neurotoxicity is dithiocarbamate-based fungicides. Case reports initially associated exposure to maneb, a widely used fungicide in this class, with the development of parkinsonism in humans (Ferraz et al. 1988; Meco et al. 1994). A rat model was recently created by direct infusion of maneb into the lateral ventricles (Zhang et al. 2003). *In vitro* studies indicate that the dopaminergic neurotoxicity of maneb may be associated with its ability to inhibit the activity of complex III in the mitochondrial respiratory chain (Zhang et al. 2003). Fitsanakis et al. (2002) had earlier proposed that the dopaminergic neurotoxicity of maneb might be associated with its ability to facilitate catecholamine oxidation. Furthermore, besides being toxic to dopaminergic neurons by itself, repeated systemic administration of maneb and paraquat to mice induced a synergistic reduction in ST dopamine content, degeneration of SN dopaminergic neurons, and development of motor behavioral abnormalities (Thiruchelvam et al. 2000a, 2000b). Neonatal exposure to both maneb and paraquat also increased the susceptibility of the nigrostriatal dopaminergic system to rechallenge with the same agents during adulthood (Thiruchelvam et al. 2002).

A third class of insecticides whose environmental exposure has been associated with increased incidence of PD includes the naturally occurring and commonly used insecticide rotenone. Rotenone is known to be a specific inhibitor of mitochondrial complex I (Earley and Ragan 1984). Because a defect in mitochondrial complex I is a well-documented feature of idiopathic PD (Swerdlow et al. 1996), rotenone was suspected to be a dopaminergic neurotoxin. Intracerebral application of rotenone had earlier been shown to damage the nigrostriatal dopaminergic pathway in rats (Heikkila et al. 1985). Initial attempts to systemically administer rotenone to rats resulted in damage to ST dopaminergic fibers but not

Table 2. Pesticides and dopaminergic neurotoxicity.

Pesticide	Features of toxicity	Animal model
Pyridinium (paraquat)	DA depletion, TH–positive neuron loss, behavior	Rat
Dithiocarbamate (maneb)	DA depletion, TH–positive neuron loss, behavior	Rat
Complex inhibitor (rotenone)	DA depletion, TH–positive neuron loss, behavior	Rat, mouse
Organochlorine (dieldrin)	DA depletion	

Abbreviations: DA, dopamine; TH, tyrosine hydroxylase.

SN dopaminergic neurons (Ferrante et al. 1997). Later attempts to acutely or subchronically administer rotenone to mice also produced only minimal damage to dopaminergic neurons (Thiffault et al. 2000). In the last several years, however, several groups have demonstrated that continuous systemic administration of rotenone to rats reproduces key features of PD, including selective degeneration of the nigrostriatal dopaminergic system, formation of cytoplasmic inclusions in SN neurons, and movement disorders (Alam and Schmidt 2002; Betarbet et al. 2000; Hoglinger et al. 2003). In addition, chronic and subcutaneous administration of rotenone resulted in a highly selective dopaminergic damage and α-synuclein aggregation (Sherer et al. 2003b). The lack of agreement among these studies may stem from differences in the route, dosage, and/or duration of rotenone application. Mechanistically, although earlier studies had implied that rotenone might interfere with the dopamine transport mechanism in the ST (Bougria et al. 1995; Marey-Semper et al. 1993), recent studies suggest that inhibition of mitochondrial complex I activity and facilitation of α-synuclein aggregation may be closely associated with rotenone's selective dopaminergic neurotoxicity (Betarbet et al. 2000; Lee et al. 2002; Sherer et al. 2002; Uversky et al. 2001). It remains to be determined whether typical human exposure to pesticides alone is likely to account for the many cases of PD. Of particular relevance may be the synergistic dopaminergic neurotoxicity observed with the combination of low levels of multiple neurotoxicants, including rotenone and LPS (Gao et al. 2003) and paraquat and maneb (Thiruchelvam et al. 2000b).

The fourth class of pesticides with potential dopaminergic neurotoxic effect consists of the organochlorine pesticides that include dieldrin. The neurotoxic and dopamine-depleting effects of dieldrin were initially observed in intoxicated ducks, doves, and rats (Heinz et al. 1980; Sharma et al. 1976; Wagner and Greene 1978). Elevated levels of residual dieldrin also have been detected in the brains of PD patients (Corrigan et al. 2000; Fleming et al. 1994). In primary mesencephalic cultures, dieldrin exhibited a selective dopaminergic neurotoxicity (Sanchez-Ramos et al. 1998) that might be mediated by its ability to induce ROS formation and lipid peroxidation as well as by its ability to promote α-synuclein fibril formation (Kitazawa et al. 2001; Uversky et al. 2001).

In addition to the above-mentioned organochlorine pesticides, case reports have associated development of parkinsonism with exposure to organophosphorus insecticides (Bhatt et al. 1999; Davis et al. 1978; Muller-Vahl et al. 1999). Administration of dichlorvos or chlorpyrifos to rats reduced catecholamine content and locomotor activity (Ali et al. 1979, 1980; Karen et al. 2001). It remains to be determined whether organophosphates, as well-characterized inhibitors of acetylcholinesterase, possess any selective dopaminergic neurotoxicity.

Although not used as insecticides, the impact of polychlorinated biphenyls (PCBs), widely used in industrial settings, on the dopaminergic system is worth mentioning. Postmortem analysis has revealed elevated levels of PCBs in PD brain (Corrigan et al. 1998). As with dieldrin, PCBs were found to deplete dopamine in cell cultures and in animals (Seegal et al. 1990). The sheer number of the PCB structurally related analogs (Shain et al. 1991) and the broad range of their systemic toxicity (Chu et al. 1995) have made it difficult to mechanistically associate a particular variety of PCB with selective dopaminergic toxicity (Choksi et al. 1997; Mariussen et al. 2001).

Two potentially important issues concerning exposure to pesticides and the development of PD in humans should be addressed. First, elevated levels of certain pesticides found in the brains of PD patients may be merely a reflection of their rural living and well-water drinking. It does not constitute a cause–effect relationship between pesticide exposure and development of PD. Experimental models using individual pesticides have been extremely valuable for us to evaluate the neurotoxic effects of those toxicants at relatively high doses. Perhaps more relevant to the probing of the impact of pesticides on the dopaminergic system in humans are the studies in which multiple agents were employed at subtoxic concentrations, such as the combination of rotenone and LPS and of paraquat and maneb (Gao et al. 2003; Thiruchelvam et al. 2000b). Clearly, additional *in vitro* and *in vivo* studies and possibly epidemiologic studies in this direction will be most informative.

The second issue relates to the selective dopaminergic neurodegeneration as a result of systemic exposure to pesticides. Current explanations for the elevated vulnerability of SN dopaminergic neurons, compared with neurons in other regions, to oxidative insults include a reduced antioxidant capacity, increased content of iron, high content of oxidation-prone dopamine, and potential defect in mitochondrial complex I (Greenamyre et al. 1999; Jenner and Olanow 1998). It remains to be determined why dopaminergic neurons in the SN, but not those in the vicinity (i.e., ventral tegmental area), are first and foremost lost in the course of the degenerative process. One possibility could that the nature and density of microglia in both regions may be different—that those in the SN are more responsive (in addition to a higher density) to stimulation by neurotoxicants or to neuronal injuries induced by the initial assault on neurons. Therefore, the microgliosis, either as a result of direct stimulation or as a consequence of neuronal injury, presents a much more harmful microenvironment to dopaminergic neurons in the SN. By the same token, neurons in other brain regions are less sensitive to the same insults, compared with SN dopaminergic neurons. Although experimental data are lacking to demonstrate the nature of microglia in different brain regions, studies have shown that, at least in rodents, the midbrain region has a higher density of microglia than other regions examined (Kim et al. 2000; Lawson et al. 1990).

The Role of Glial Cells in Pesticide-Induced Dopaminergic Neurodegeneration

Research on the dopaminergic neurotoxicity of pesticides has traditionally focused on the direct effect of those agents on neurons. However, it has recently been demonstrated that microglia actively participate in the rotenone-induced degeneration of dopaminergic neurons in mesencephalic neuron–glia cultures (Gao et al. 2002a). In the absence of microglia, rotenone exhibited a markedly reduced toxicity to dopaminergic neurons. In the presence of microglia, however, low nanomolar concentrations of rotenone were able to activate microglia to release superoxide free radicals and facilitate the degeneration of dopaminergic neurons. Further studies using enzyme inhibitors suggested that the rotenone-induced release of superoxide was mediated by microglial NADPH oxidase (Gao et al. 2002a), a primary source of superoxide generation in the immune cells of both the peripheral and the central nervous systems (Babior 1999). The detailed molecular mechanism responsible for this rotenone-stimulated activation of microglial NADPH oxidase, however, remains to be elucidated. Nevertheless, the observation of an active participation of microglia has significantly advanced our understanding of the dopaminergic neurotoxicity of rotenone, because rotenone had previously been thought to act exclusively as an inhibitor of neuronal mitochondrial complex I. Neuronal death was thought to be a consequence of the inhibition of mitochondrial complex I, which then led to a reduction in the energy supply and subsequent collapse of the mitochondrial membrane potential. In addition to the *in vitro* observation for the active participation of microglia in rotenone neurotoxicity, in rotenone-infused rats microglial activation has recently been reported to precede dopaminergic neurodegeneration (Sherer et al. 2003a).

Besides being able to activate microglia to release free radicals, rotenone and LPS have recently been reported to exert synergistic dopaminergic neurotoxicity (Gao et al. 2003). Exposure to a combination of individually nontoxic concentrations of rotenone and LPS has

significantly increased dopaminergic neurodegeneration in mesencephalic neuron–glia cultures. The observed synergistic neurotoxicity between a pesticide (i.e., rotenone) and an inflammogen (i.e., LPS; Gao et al. 2003), together with observations of synergistic neurotoxicity among different classes of pesticides (i.e., paraquat and maneb; Thiruchelvam et al. 2000b), is consistent with a multifactorial hypothesis of PD etiology. Additional studies are needed to examine the effect of exposure to multiple environmental neurotoxicants on the nigrostriatal dopaminergic pathway.

Microglial Activation and Reactive Microgliosis: A Self-Propelling Cycle of Neuroinflammation that Fuels the Progressive Dopaminergic Neurodegeneration

The potential role that microglia play in the dopaminergic neurodegenerative process suggests that their contribution to the death of dopaminergic neurons includes the release of a variety of neurotoxic factors in response to immunologic stimuli. Similar to macrophages, their peripheral counterpart, microglia, as the first line of defense in the brain, can be directly activated by invading pathogens.

On the other hand, it is well documented that microglia become activated after the occurrence of neuronal injuries. Although a variety of soluble factors released from injured neurons have been proposed to be the potential stimulators of reactive microgliosis (Giulian and Ingeman 1988; Giulian et al. 1991; Raivich et al. 1999), loss of cell–cell contact between neurons and glial cells may also result in microglial activation (Chang et al. 2000a, 2000b). For example, Chang et al. demonstrated that neurons act to suppress the reactivity of glial cells through a potential dimerization of the neural cell adhesion molecules expressed on the surface of both cell types (Chang et al. 2000a, 2000b). Neurons may be able to negatively regulate the reactivity of glial cells through other types of cell–cell contact such as the CD200 receptor–ligand interaction (Neumann 2001), analogous to CD200's role in the negative regulation of myeloid cells (Barclay et al. 2002). Therefore, exposure to infectious agents such as viruses and bacteria can directly lead to the activation of glial cells, especially the microglia. On the other hand, glial cells also can be activated as a reactive response to neuronal injuries inflicted by injuries or agents such as certain pesticides that can directly damage neurons. Furthermore, certain environmental toxicants, such as rotenone, can induce neuronal damage and at the same time activate microglia. In essence, regardless of the nature of the initiating factors, a cycle may exist: Microglial activation leads to neurodegeneration; neuronal injury, in turn, leads to reactive glial activation, which further exacerbates neurodegeneration. This self-propelling cycle of brain inflammation may be particularly damaging to the SN dopaminergic neurons, which reside in a microglia-rich region in the brain and which are particularly vulnerable to oxidative stress. The continuing presence of this cycle over time—plus the possible involvement of additional uncharacterized factors, intrinsic and/or over many years—leads to a massive degeneration of the nigrostriatal dopaminergic pathway and the development of symptomatic PD (Figure 2).

Concluding Remarks

Idiopathic PD is an age-related disease that may represent the final outcome of interactions among a variety of intrinsic and environmental factors. Inflammation in the brain clearly plays an active role in the pathogenesis of PD. Understanding the nature of those complex interactions may be a prerequisite for success in our quest for effective strategies to halt the progressive neurodegenerative process of idiopathic PD.

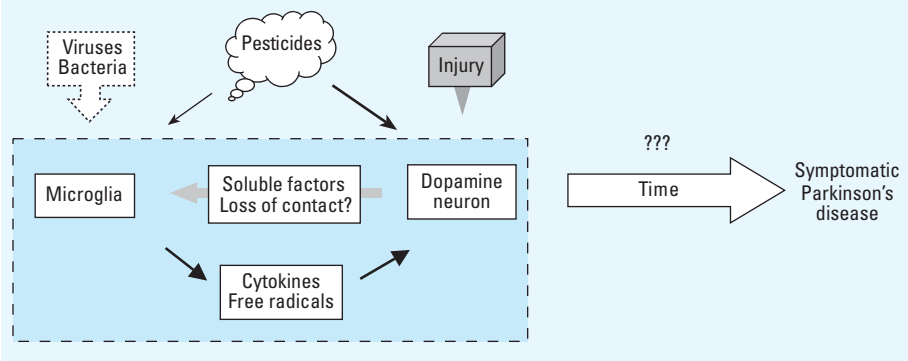

Figure 2. Schematic representation of the hypothesis for the self-propelling microglial activation as a driving force of the progressive dopaminergic neurodegeneration. Environmental factors either can directly activate glial cells or can induce neuronal injuries. Uncharacterized factors related to the initial neuronal injuries induce the reactive response of glial cells. Activated glial cells produce a variety of proinflammatory and neurotoxic factors that exacerbate neuronal damage. This feed-forward cycle of glial activation and neurodegeneration, over time, results in sufficient degeneration of the nigrostriatal dopaminergic pathway to lead to the development of symptomatic PD. The involvement of additional factors, intrinsic (e.g., genes) or environmental (toxicants), in this process need not be excluded.

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